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Fear and distress disorders as predictors of heart disease: a temporal perspective

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Short title

Fear and distress disorders and heart disease

Conflicts of interest

In the past 3 years, Dr. Stein has received research grants and/or consultancy honoraria from AMBRF, Biocodex, Cipla, Lundbeck, National Responsible Gambling Foundation, Novartis, Servier, and Sun. In the past three years, Dr. Kessler has been a consultant for Hoffman-La Roche, Inc., Johnson & Johnson Wellness and Prevention, and Sonofi-Aventis Groupe. Dr. Kessler has served on advisory boards for Mensante Corporation, Johnson & Johnson Services Inc. Lake Nona Life Project, and U.S. Preventive Medicine. Dr. Kessler is a co-owner of DataStat, Inc.

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Abstract

Objective

Few studies have been able to contrast associations of anxiety and depression with heart disease. These disorders can be grouped in fear and distress disorders. Aim of this study was to study the association between fear and distress disorders with subsequent heart disease, taking into account the temporal order of disorders.

Methods

Twenty household surveys were conducted in 18 countries (n=53791; person years=2,212,430). The Composite International Diagnostic Interview assessed lifetime prevalence and age at onset of disorders, and respondents were categorized into categories based on the presence and timing of fear and distress disorders. Heart disease was indicated by self-report of physician-diagnosed heart disease or self-report of heart attack, together with year of onset. Survival analyses estimated associations between disorder categories and heart disease.

Results

Most respondents with fear or distress disorders had either pure distress or pure fear (8.5% and 7.7% of total sample), while fear preceded distress in the large majority of respondents with comorbid fear and distress (3.8% of total sample). Compared to the “no fear or distress disorder” category, respondents with pure fear disorder had the highest odds of subsequent heart disease (OR:1.8;95%CI:1.5-2.2;p<.001) and compared to respondents with pure distress disorder, these respondents were at a significantly increased risk of heart disease (OR:1.3;95%CI:1.0-1.6;p=0.020).

Conclusion

This novel analytic approach indicates that the risk of subsequent self-reported heart disease associated with pure fear disorder is significantly larger than the risk associated with distress

disorder. These results should be confirmed in prospective studies using objective measures of heart disease.

Keywords: Anxiety; classification; depression; distress; fear; heart disease

Introduction

Most attention to the association between psychosocial factors and heart disease has been directed to depression, with several meta-analyses showing that depression is related to an increased risk of coronary heart disease (CHD) (Nicholson et al., 2006; Van der Kooy et al., 2007). Several studies showed that anxiety is also related to the development of CHD, which was confirmed in a first meta-analysis on this topic (Roest et al., 2010). Most anxiety studies have focused on elevated symptoms of anxiety. However, generalized anxiety disorder (GAD) was related to subsequent cardiovascular and all-cause mortality in Vietnam veterans, although after adjustment for covariates the association remained statistically significant for all-cause mortality only (Phillips et al., 2009). Posttraumatic stress disorder (PTSD) has also been shown to increase the risk of CHD and heart disease mortality in Vietnam veterans (Boscarino 2008; Vaccarino et al., 2013). In addition, a recent systematic review and meta-analysis summarizing results of studies with varied study designs, found a significant association between panic disorder (PD) and incident CHD (Tully et al., 2015a). Indeed anxiety disorders might even be more strongly related to the development of CHD than depression. Early onset anxiety disorder, but not depressive disorder, predicted the development of CHD in young Swedish men over a period of 37 years (Janszky et al., 2010). Also, in the World Mental Health (WMH) Surveys, the risk of subsequent heart disease was stronger for PD, specific phobia, and PTSD than for depression after adjustment for mental disorder comorbidity (Scott et al., 2013), although it was not tested whether this difference between anxiety disorders and depression was statistically significant.

Depressive and anxiety disorders have a considerable overlap (Clark & Watson 1991; Watson 2005). In an empirically based model, Watson grouped anxiety and depressive disorders into fear and distress disorder categories since these groups appear to be distinctly different from each other (Watson 2005), a distinction that has subsequently been empirically confirmed

(Kessler et al., 2012a; Eaton et al., 2013). In this model, fear disorders (panic disorder, agoraphobia without panic, social anxiety disorder (SAD), specific phobia) are distinguished from distress disorders (depression, dysthymia, and GAD). In this model GAD is classified as a distress disorder since it is more strongly linked to depression than to fear disorders, which are characterized by phobic fear and somatic arousal (Clark & Watson 1991; Watson 2005; Brown & McNiff 2009; Den Hollander-Gijsman et al., 2010). Phobic fear and somatic arousal may be particularly strongly related to the development of heart disease and adverse prognosis in patients with CHD (Albert et al., 2005; Watkins et al., 2010; Nabi et al., 2010; Roest et al., 2014). Therefore, categorizing depressive and anxiety disorders into fear and distress disorders may be more useful than comparing anxiety and depressive disorders, or examining all disorders separately, when investigating the association between these disorders and heart disease.

Few studies have considered the role of anxiety disorders when examining the association between depressive disorder and heart disease and none have examined whether fear disorders explain the association between distress disorders and development of heart disease. The median age of onset of fear disorders is much earlier than for distress disorders, especially for specific phobia and SAD (Kessler et al., 2005). Also, traumatic life experiences, which can lead to PTSD, often occur for the first time in childhood/adolescence (Kessler et al., 2012b). In addition to occurring at an earlier age, fear disorders also have a more persistent course than distress disorders, and fear disorders, especially phobias and panic, may even predict the first onset of a distress disorder (Wittchen et al., 2003; Mathew et al., 2011; Kessler et al., 2012a). These characteristics of fear disorders give rise to the possibility that the association with subsequent heart disease is stronger for fear disorders than for distress disorders since anxious individuals would experience a more long-term exposure to mediating mechanisms.

As a result (part of) the observed association between distress disorders and CHD may be actually due to the comorbidity with fear disorders.

The aim of the current study is to examine the association between (any) fear and (any) distress disorder with subsequent onset of heart disease, while taking into account the temporal order of disorders. We hypothesize that both fear and distress disorders are predictors of subsequent onset of heart disease, but the risk associated with pure (non-comorbid) fear disorder, or fear disorder preceding distress disorder, will be stronger than the risk associated with pure (non-comorbid) distress disorder.

Method

Samples and procedures

This study used data from 20 of the WMH general population surveys. Most surveys were based on nationally representative household samples; the others were representative of urban areas (Colombia, Mexico, PRC Shenzhen, Japan). Interviews took place between 2001 and 2012 (see table 1). In most countries the interview was divided in two parts to reduce respondent burden. All respondents completed Part 1, which included the diagnostic assessment of most mental disorders, including fear and distress disorders. All Part 1 respondents who met lifetime criteria for any mental disorder and a probability sample of respondents without mental disorders were administered Part 2 that, among others, assessed physical conditions. Part 2 responses were weighted by the inverse of their probability of selection into Part 2. Further details about WMH sampling and weighting are available elsewhere (Heeringa et al., 2008).

Analyses in the current study are based on the weighted Part 2 subsample ($n = 53,791$; person years = 2,212,430). Additional weights were used to adjust for differential probabilities of selection within households and to match population distributions on socio-demographic and

geographic data. Measures taken to ensure data accuracy and cross-national consistency are described elsewhere (Kessler & Ustün 2004; Kessler & Ustün 2008).

Ethics statement

Procedures for human subject protection were approved and monitored for compliance by the institutional review boards of the organizations coordinating the surveys. Informed consent was obtained before the interviews commenced (Kessler & Ustün 2008).

Measures

Mental disorders

Lifetime history, and age of onset, of DSM-IV mental disorders were assessed using the WMH survey version of the WHO Composite Diagnostic Interview (CIDI 3.0) (Kessler & Ustün 2004). The interview included probing strategies to increase reliability of the age of onset of disorders (Kessler & Ustün 2004). Fear disorders included PD, agoraphobia without PD, SAD, specific phobia, and PTSD because of their association with phobic fear and somatic arousal (Clark & Watson 1991; Brown & McNiff 2009; Den Hollander-Gijsman et al., 2010), which we hypothesized as driving factors for an association with subsequent heart disease. Distress disorders included major depressive episode/dysthymia and GAD.

Respondents were also assessed for obsessive-compulsive disorder, bipolar disorder broad (I, II and sub threshold); substance use disorders (alcohol abuse and dependence, drug abuse and dependence); and impulse control disorders (intermittent explosive disorder, bulimia nervosa, and binge eating disorder). CIDI diagnoses of lifetime history of these mental disorders have shown generally good concordance with diagnoses based on blinded clinical interviews (Haro et al. 2006).

Heart disease

Lifetime presence of heart disease was assessed from questions adapted from the US Health Interview Survey. Respondents were asked whether a doctor or other health professional had ever told the participant they suffered from heart disease (“Did a doctor or other health professional ever tell you that you had heart disease?”). Respondents were also asked whether they ever had a heart attack (“Have you ever had a heart attack?”). If respondents were ever told to have heart disease, or responded they ever had a heart attack, they were classified as having a history of heart disease. Respondents were asked how old they were when they were first diagnosed or had a heart attack and this year was used as age of onset of heart disease (if both were endorsed the youngest age was used). Consistent with previous publications on associations between mental disorders and various somatic diseases in the WMH surveys (Aguilar-Gaxiola et al., 2016; O'Neill et al., 2014; Rapsey et al., 2015; Scott et al. 2011; Scott et al. 2013; Swain et al., 2015), only adult-onset heart disease (age ≥ 21 years) was investigated in this study in order to exclude cases of childhood onset heart disease.

Childhood family adversities

Two previous reports of the WMH surveys showed associations between childhood family adversities and somatic conditions (Scott et al. 2008; Scott et al. 2011), which may confound the association between fear and distress disorder categories with subsequent heart disease. All surveys included questions on physical and sexual abuse occurring within the family context before age 18 (details regarding the assessment of these adversities can be found in Scott et al. 2008).

Statistical analysis

Discrete-time survival analyses (Singer & Willett 1993) with person-year as the unit of analysis were used to investigate associations between fear and distress disorder categories and the subsequent onset of heart disease. A person-year data set was created in which each

year in the life of each respondent up to and including the age of onset of heart disease or their age at interview (whichever came first) was treated as a separate observational record, with the year of heart disease onset coded 1 and earlier years coded 0 on a dichotomous outcome variable. Those reporting heart disease onset before age 21 ($n=423$, 11.4% of the total number reporting heart disease) were excluded from the analyses. Using information on age of onset of fear and distress disorder, respondents were categorized in 6 exclusive groups: respondents with pure fear disorder, respondents with pure distress disorder, respondents with fear disorder preceding distress disorder, respondents with distress disorder preceding fear disorder, respondents with a simultaneous onset of fear and distress disorder, and respondents with neither a distress nor a fear disorder. Initially all respondents were coded 1 on “no fear and no distress” and this variable was switched off one year after onset of the first disorder in the other categories, and respondents were coded 1 on their respective category from that point in time. This time lag of 1 year ensured that inclusion in the fear or distress categories in the same year as heart disease onset did not count as a predictor. Only person-years up to the diagnosis of heart disease were analyzed so that only fear or distress episodes occurring prior to the onset of heart disease were included in the predictor set. Logistic regression analysis was used to estimate associations with the survival coefficients presented as odds ratios, indicating the relative odds of heart disease onset in a given year for an individual in a specific category compared to individuals with neither a distress nor a fear disorder (reference group). When examining whether differences between pure fear disorder and fear preceding distress disorder were significantly different from pure distress disorder, we changed the reference group to the group consisting of respondents with pure distress disorder.

Covariates were selected a priori based on the literature and previous reports of the WMH surveys. In the first model analyses are adjusted for person-years, country, age-cohorts, and gender. The second model additionally adjusted for time-varying education (number of years)

and smoking (never/ever/current) since these variables could be confounders in the associations between fear and distress disorder categories and subsequent heart disease. In the third model, results were additionally adjusted for childhood family adversity. Finally, in the fourth model total number of comorbid disorders not included in the fear/distress categories (i.e. bipolar disorder, obsessive-compulsive disorder, impulse-control disorders, and substance use disorders) was added to the model. We examined whether there were gender differences in the association between fear and distress disorders with subsequent heart disease by including an interaction term between disorder categories and gender in the first model. Consistent with a previous study on WMH data there were no significant interactions (Scott et al. 2013) (results not shown, available upon request). It could be hypothesized that differences for associations with heart disease exist for disorders on the basis of whether acute fear can be avoided (i.e. agoraphobia without PD, social phobia, specific phobia) or not (i.e. PD, PTSD) since somatic arousal may be specifically linked to the latter (Brown & McNiff 2009). Therefore, in sensitivity analysis, we examined whether respondents with pure phobia and pure PD or PTSD were at an increased risk of subsequent heart disease compared with respondents without pure PD, pure PTSD, or pure phobia.

Because the data were clustered and weighted, standard errors were estimated using the Taylor series linearization method (Wolter 1985) implemented in the SUDAAN software system (11.0) (Research Triangle Institute 2002). Significance tests were all evaluated at the 0.05 level using two-sided tests.

Results

Sample characteristics

The weighted average response rate across surveys was 69.0%. The characteristics of the sample are presented per country in table 1 together with the number of respondents who

reported to have heart disease and the (weighted) prevalence of a history of heart disease. This prevalence ranged from 1.7% in Peru to 14.2% in Romania. Prevalence of heart disease in the total sample was 5.9%.

Prevalence of fear and distress disorder

The prevalence of fear disorder was 13.3% (SE: 0.2) and the prevalence of distress disorder was 14.0% (SE: 0.2) in the total sample. Table 2 includes prevalence rates of the fear and distress disorder categories taking into account comorbidity between fear and distress disorders and the temporal order of disorders. Most respondents had pure distress disorder (8.5%), followed by respondents with pure fear disorder (7.7%), respondents with fear disorder preceding distress disorder (3.8%), respondents with a simultaneous onset of distress and fear disorder (0.9%) and respondents with distress disorder preceding fear disorder (0.8%).

Associations between fear and distress disorder categories with subsequent onset of heart disease

After adjusting for person-years, country, age-cohorts and gender (model 1), all categories predicted subsequent heart disease (ORs: 1.5-2.0) compared with the category consisting of respondents with no distress and no fear disorder (Table 3). Additional adjustment for smoking and education (model 2) did not change the results, but after additional adjustment for childhood adversity (model 3) the relationship between simultaneous onset of fear and distress disorder lost statistical significance. In the final model that further adjusted for number of comorbid mental disorders the ORs were attenuated but remained statistically significant. ORs were largest for pure fear (OR: 1.8; 95% CI: 1.5-2.2) and fear preceding distress disorder (OR: 1.6; 95% CI: 1.4-2.0) and lower for distress disorder preceding fear disorder (OR: 1.5; 95% CI: 1.0-2.2) and pure distress disorder (OR: 1.4; 95% CI: 1.2-1.7).

After changing the reference group to respondents with pure distress disorder, respondents with pure fear disorder were at a significantly increased risk of heart disease (OR: 1.3; 95% CI: 1.0-1.6) while the estimates did not reach statistical significance for fear disorder preceding distress disorder (OR: 1.2; 95% CI: 0.9-1.5) and distress disorder preceding fear disorder (OR: 1.1; 95% CI: 0.7-1.6) (Table 3).

Subtypes of pure fear disorder and subsequent heart disease

Table 4 shows results for the sensitivity analysis that examines the association between pure PD/PTSD and pure phobia with subsequent heart disease. After adjustment for persons-years, country, age-cohorts, education, smoking, and childhood family adversity, both pure PD/PTSD (OR: 1.9; 95% CI: 1.5-2.5) and pure phobia (OR: 1.6; 95% CI: 1.4-1.8) were significantly related to heart disease.

Discussion

The results of this study suggest that fear disorders are more strongly related to the development of heart disease than distress disorders. While both fear and distress disorders were predictive of subsequent self-reported heart disease after adjustment for sociodemographic factors, childhood family adversities and comorbid mental disorders, the effect estimates were highest for pure fear disorder and fear preceding distress disorder. When compared to pure distress disorder this difference was significant for pure fear disorder, although it was not significant for fear preceding distress disorder. However, this may be the result of reduced statistical power since the group consisting of individuals with pure fear disorder was larger than the group consisting of individuals with fear preceding distress disorder.

Fear disorders, including PD, phobias, and PTSD have an early age of onset (Kessler et al., 2005) and are generally persistent over time (Kessler et al., 2012b), suggesting that anxious

individuals experience long-term exposure to mechanisms potentially leading to heart disease. This might explain the stronger adverse relationship of fear disorder with heart disease when compared to distress disorder. Fear disorders are further specifically characterized by underlying symptom dimensions of somatic arousal and phobic fear. These characteristics have been repeatedly shown to predict incident CHD (Albert et al., 2005; Nabi et al., 2010) and CHD prognosis (Watkins et al., 2010; Roest et al., 2014), although not all study results have been consistent. In a relatively small sample of patients who were assessed for anxiety and depression before undergoing coronary artery bypass graft surgery, neither fear disorder (a cluster including PD, agoraphobia and SAD) nor anxious arousal was predictive of cardiovascular and cerebrovascular events. Only GAD, and not distress disorder (a cluster including GAD, major depression, dysthymia and PTSD), was related to the combined endpoint (Tully et al., 2015b). Similarly, in the Netherlands Health Survey and Incidence Study-2 (NEMESIS-2), Batelaan et al., (2014) examined types of anxiety disorders (worry-type, panic-type, and phobic-type), and found that only GAD was significantly related to incident cardiovascular disease (Batelaan et al., 2014). In contradiction to these findings, in a previous study of the WMH surveys GAD was only weakly associated with subsequent heart disease (Scott et al., 2013). These conflicting results for GAD could potentially be the result of GAD cross loading on both the fear and distress dimension (Eaton et al., 2013).

Mechanisms

Our finding that (pure) fear disorder was a stronger predictor of heart disease onset than (pure) distress disorder is possibly indicative of a specific link between fear disorders and CHD. However, at the moment only preliminary evidence exists for such a specific effect. One suggested mediator of the association between somatic hyper arousal and CHD is dysregulation of the autonomic nervous system. However, it appears that the association between anxiety disorders and reduced heart rate variability is, at least partly, mediated or

confounded by the use of antidepressant medications (Licht et al., 2009) and adverse health behaviors, such as smoking, alcohol overuse and sleep disturbance (Dennis et al., 2014). Since physiological and behavioral factors that may mediate associations between mental disorders and heart disease are interdependent, additional research should preferably study these factors in networks instead of in isolation (de Jonge & Roest 2012).

Strengths and limitations

An important strength of the current study is the use of a theoretical framework to examine associations between fear and distress disorders with subsequent heart disease. The use of liability dimensions over specific disorders has previously been demonstrated by Eaton et al. (2013), who showed that liabilities of distress and fear, and not disorder-specific variation predicted health outcomes in a nationally representative sample of the US population. A potential limitation of the current study is that our decision to include PTSD as a fear disorder may be questionable. Studies examining the structure of mental disorders (e.g. Krueger 1999, Vollebergh et al., 2001) often did not include PTSD (Carragher et al., 2015). In other cases, PTSD was assigned to the distress category (Cox et al., 2002; Kessler et al., 2012a; Slade & Watson 2006). Also, a recent analysis on data from the WMH surveys classified PTSD as a distress disorder, although PTSD cross-loaded on both the fear and distress factor (Wardenaar et al., in press). Indeed, factor loadings for PTSD have been found to be relatively low (Cox et al., 2002; Slade & Watson 2006; Wardenaar et al., in preparation) and it has been hypothesized that symptoms of emotional numbing may drive the relationship between PTSD and distress disorders (Slade & Watson 2006). We decided to include PTSD in the fear category because of its association with somatic arousal (Brown & McNiff 2009), one of the specific features we hypothesized to be responsible for the increased risk of heart disease onset. It is important that future research further improves the transdiagnostic model of mental disorders, not only by including additional disorders, but also other factors associated with

psychopathology, such as neurobiological systems and genetic variance (Carragher et al., 2015; Krueger & Eaton 2015). Another limitation of the current study is that only DSM-IV diagnoses were assessed and we could not examine the dimensional aspect of fear and distress symptomatology in association with incident heart disease. Combining a dimensional approach to psychopathology with information from neurobiological measures is one of the main components of the RDoC project, which aims to improve future diagnosis of psychiatric disorders (Cuthbert 2014; Kozak and Cuthbert 2016). Other limitations with respect to the WMH surveys include the retrospective assessment of mental disorders, which probably led to an underestimation of the prevalence of mental disorders and potentially to inaccuracies regarding age of onset information (Moffitt et al., 2010; Takayanagi et al., 2014). In addition, a subjective measure of heart disease (self-report of physician-diagnosed heart disease and self-report of heart attack) was used, which may have introduced misclassification of patients regarding our endpoint. However, in general, individuals are more likely to accurately report medical conditions than mental disorders (Takayanagi et al., 2014). Further, although symptoms of fear disorder overlap with symptoms of heart disease, and individuals with GAD may be more likely to worry about heart disease, individuals were asked whether they received a diagnosis of heart disease, which probably reduced over reporting of the condition in anxious individuals. Therefore, we do not expect this to account for our observation that fear disorders are more strongly associated with heart disease than distress disorders, especially since GAD was included in the distress disorder category. Furthermore, although we used survival analysis based on age of onset information, our data was cross-sectional, and future prospective studies are needed to confirm our findings. Future research should also replicate the difference between the associations between (pure) fear and (pure) distress disorder with heart disease since effect sizes were not very large. Finally, in this study only self-report of physician-diagnosed heart disease and self-report of heart attack, and not

cardiac mortality could be examined as an endpoint. Since previous studies found a relationship between symptoms of phobic anxiety and ventricular arrhythmias and sudden cardiac death (Albert et al., 2005; Watkins et al., 2010) the results reported for fear disorders are likely to be conservative.

Clinical implications

Anxiety has been proposed as a target for primary prevention of CHD (Thurston et al., 2013). The current study suggests that particularly individuals with (pure) fear disorders could potentially benefit from psychiatric treatment in terms of CHD onset and progression. Various treatments options are available for individuals suffering from fear disorders, the most well-known ones being pharmacological treatment (Roest et al., 2015) and cognitive behavior therapy (Hoffman & Smits 2008), which could be offered in a collaborative care framework (Huffman et al., 2014). However, before designing trials aimed at improving cardiac risk factors in anxious individuals using anxiety treatments, more research is arguably needed to study characteristics of the subgroup of individuals who are most at risk of incident CHD and ideally mechanisms involved in this association should be identified.

Conclusions

The main finding of this study was that dividing anxiety and depressive disorders into fear and distress disorder, while taking the temporal order of disorders into account, provided important information regarding the association of these conditions with subsequent self-report of physician-diagnosed heart disease or self-report of heart attack. While most disorder categories were related to development of heart disease, the risk was significantly higher for individuals with fear disorder only, compared with individuals with distress disorder only. Our findings thus suggest that the focus on depression in the context of heart disease should be extended to fear disorders. This attention is warranted in order to examine which

mechanisms are more strongly activated in the case of fear compared with distress, or whether specific mechanisms exist that link fear disorder to the development of heart disease.

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